Lemierre syndrome: Current evidence and rationale of the Bacteria-Associated Thrombosis, Thrombophlebitis and LEmierre syndrome (BATTLE) registry

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Review Article

Lemierre syndrome: Current evidence and rationale of the Bacteria-Associated Thrombosis, Thrombophlebitis and LEmierre syndrome (BATTLE) registry

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ABSTRACT

Lemierre syndrome is a rare but potentially fatal condition characterized by septic thrombophlebitis of the head and neck district, preferentially affecting adolescents and young adults and manifesting as a complication of a local bacterial infection – typically, a pharyngotonsillitis or an abscess. It is historically associated with the Gram-negative anaerobic rod *Fusobacterium necrophorum* and with thrombophlebitis of the internal jugular vein. However, its definition has never been firmly established, and its spectrum within the continuum of bacteria-associated thrombophlebitis may be larger than what presumed so far. Recent evidence suggests that its prognosis remains serious even one hundred years after its first description, with considerable rates of in-hospital complications, death, and long-term sequelae. There are no specific guidelines on its management other than usual antibiotic stewardship, with ongoing debate on the potential role of therapeutic-dose anticoagulation.

We provide an overview of current evidence on the definition, epidemiology, clinical presentation, prognosis and management of this condition and present the background and rationale of the Bacteria-Associated Thrombosis/Thrombophlebitis and LEmierre syndrome (BATTLE) registry: an ambispective, disease-specific, non-population based, multicentre clinical registry of global reach and multidisciplinary scope, specifically designed to address the limitations of current evidence and to provide patients and physicians with clinically viable information to guide management and improve the outcomes of those affected by these conditions.

1. Current evidence on Lemierre syndrome

First described approximately one century ago, Lemierre syndrome, a rare, but potentially fatal form of septic thrombophlebitis, is still poorly understood. With evidence suggesting that its prognosis remains serious and its incidence, or at least the global awareness on it, is increasing, more reliable data to guide its clinical management are urgently needed. We provide an overview of the current state of evidence on this condition and present the rationale of the international Bacteria-Associated Thrombosis/Thrombophlebitis and LEmierre syndrome (BATTLE) registry.

1.1. Definition, physiopathology, and epidemiology

In 1900, the French physicians Courmont and Cade were the first to characterise a condition in which anaerobic bacteria caused an oropharyngeal infection, gained intravascular access, and produced septic pulmonary infarcts [1]. Subsequently, the Americans Goldman and Mosher (1917–1920) and the German Fränkel (1925) specifically described the transition from an initial tonsillitis to thrombophlebitis of the tonsillar veins, a septic thrombus in the internal jugular vein, and its fragmentation in septic emboli. However, they could not identify the causative agent conclusively [2,3]. Fränkel's article was referenced by the Parisian professor André Lemierre (Fig. 1) in his description of 20 cases published in the *Lancet* in 1936, which ultimately resulted in the eponym *Lemierre syndrome* from the 1980s at the earliest [4,5]. Lemierre's patients were otherwise healthy adolescents and young adults affected by a head or neck infection, often a peritonsillar, parapharyngeal or retropharyngeal abscess mimicking a simple tonsillitis, which was indeed complicated by local venous thrombosis – typically of the internal jugular vein, ultimately unleashing multiple peripheral septic emboli with subsequent abscess formation, especially in the lungs

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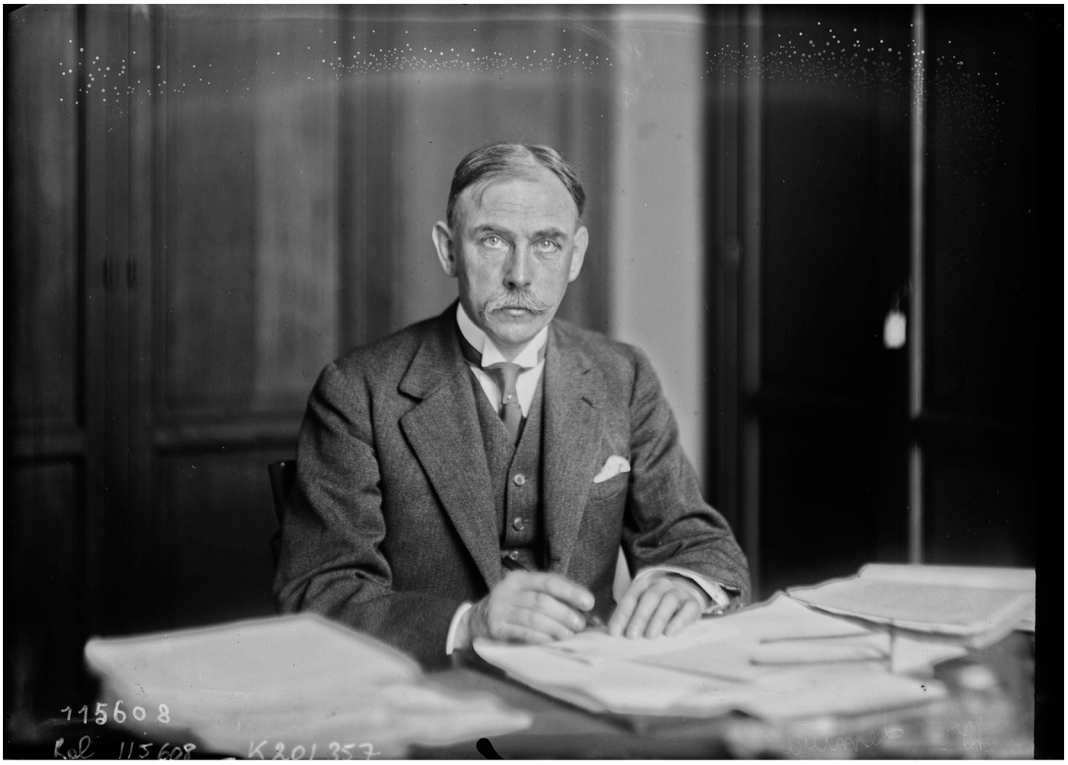

Fig. 1. Dr. André Lemierre (1875–1956), professor of Bacteriology and Infectious Diseases in Paris.
Source: gallica.bnf.fr; Bibliothéque Nationale de France/Agence Rol.

and the joints. Lemierre observed the co-occurrence of all individual disease stages and findings reported separately by his predecessors, confirming that the agent most frequently responsible for the syndrome was an anaerobic Gram-negative rod then mostly known as *Bacillus funduliformis*, which would be later renamed *Fusobacterium necrophorum*.

How the infection spreads from its initial focus to the intravascular space is uncertain. The early notion that the typical primary infection was a tonsillitis and the thrombus was usually located in the internal jugular vein initially suggested that bacteria spread through the tonsillar and peritonsillar veins [6]. As it became clear that other head or neck infections can cause the syndrome and that other vessels, including the external jugular vein or the facial vein, may be involved, other pathways were postulated, including direct extension through the fascial plane between the tonsils and the parapharyngeal space and lymphatic spread [7]. All reports from the twentieth century confirmed the syndrome's specific association with *Fusobacterium necrophorum*. Well-known in veterinary medicine because of the serious suppurative infections caused by subspecies *necrophorum* (biotype A) in cattle, this organism is most commonly found in the human oropharyngeal, gastrointestinal and female genital flora as subspecies *funduliforme* (biotype B) [5,8]. The latter subspecies' ability to cause invasive infections (*necrobacillosis*) with thrombophlebitis and distant abscess formation has been attributed to its numerous virulence factors. *Fusobacterium necrophorum funduliforme* can adhere to epithelial cells [9] and penetrate tissues by converting plasminogen into the fibrinolytic enzyme plasmin [10]. It may be able to evade the innate immune system by binding factor H [11] and by secreting a protein that inhibits leukocyte migration toward the site of infection [12]. Its ability to promote thrombus formation has been attributed to its hemagglutinin [12], which promotes platelet aggregation, or to direct activation of the contact system [13], and may also have evolved as a mean to stave off immune cells while promoting a locally anaerobic environment [12]. Heparinase may then precipitate septic embolization [14,15]. Several of these properties, however, are shared by other members of the same genus, such as *Fusobacterium nucleatum*, increasingly studied over the last few years because of its association with parodontitis and several gastrointestinal diseases [16], as well as by other genera, namely *Staphylococcus* spp., *Streptococcus* spp. and *Bacteroides* spp., frequently isolated in patients with Lemierre syndrome and cultures negative for *Fusobacterium* spp. [12,17].

Three criteria are historically used to diagnose Lemierre syndrome: (i) a primary site of infection located in the head or neck (typically, history of sore throat or anginal illness); (ii) a thrombosis or thrombophlebitis of the internal jugular vein or other vein of the head/neck district, or metastatic lesions (sometimes listed as two separate criteria); (iii) the isolation of *F. necrophorum* from blood culture or a normally sterile site. This definition is the result of considerable historical evolution [5]. While some debate remains as to whether diagnosis of Lemierre syndrome requires an oropharyngeal infection (rather than any infection of the head/neck district), cases of thrombosis or septic embolism from *Fusobacterium* spp. septicemia originating from foci outside the head and neck are generally excluded or described as “atypical” or “variant” Lemierre syndrome. There is now substantial consensus that a thrombus in the internal jugular vein does not need to be demonstrated, because a clot at this site may be easily missed, and, when present, does not seem to persist over the whole clinical course [5]. Similarly, the isolation of *Fusobacterium* spp. is not considered to be mandatory: this organism is difficult to isolate, cultures may be negative due to empiric antibiotic therapy, and other bacteria seem able to cause Lemierre syndrome [5,17]. In a recent analysis of 712 cases reported in the scientific and grey literature since 2000, which were identified using the commonly applied broad definition [7], the cases satisfying the “typical” definition (oropharyngeal infection and isolation of *Fusobacterium* spp.) only represented approximately half of the observed spectrum of the syndrome; Fig. 2 [18]. Therefore, the clinical definition of Lemierre syndrome may be considered a specific manifestation of the continuum represented by bacterial thrombophlebitis,

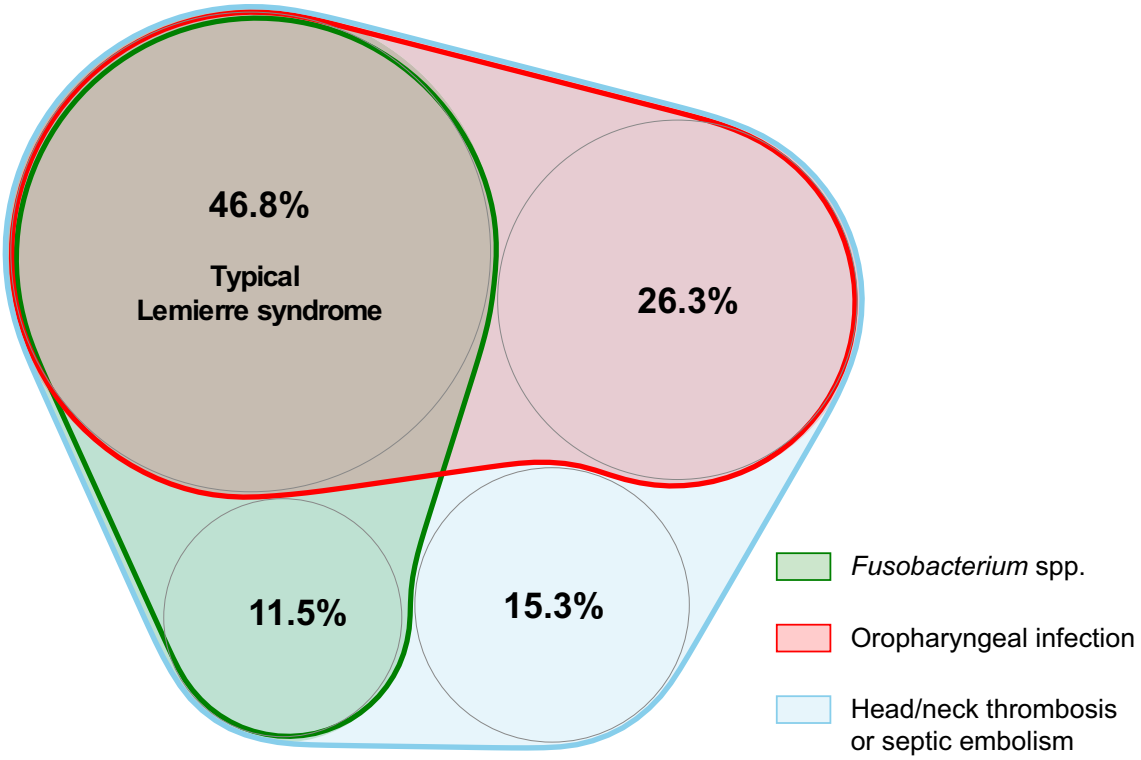

Fig. 2. Proportional area chart of the distribution of the traditional criteria for Lemierre syndrome in 712 cases described from 2000 to 2017. All patients had a primary head/neck infection and head/neck thrombosis or septic embolism, but only about half satisfied the typical definition of *Fusobacterium* spp.-associated, post-anginal thrombosis or septic embolism.

which includes conditions associated with diverse primary infections caused by several microbiological agents [17].

Lemierre syndrome is rare, but its incidence is unknown. Estimates based on country-wide or regional retrospective analyses of data from microbiology laboratories suggest an annual incidence ranging from 0.8 to 3.6 cases/million population. [19–22] However, this condition is remarkably specific to adolescents and young adults. In these age groups, estimates of the annual incidence were considerably higher, reaching 14.4 cases/million population aged 14 to 25 years (Denmark, 1998–2001) [19] and 16 cases/million population aged 15 to 19 years (Sweden, 2017) [22]. Why the syndrome affects these age groups so specifically remains a mystery. Early hypotheses attribute the age distribution to the change from a predominantly aerobic to a predominantly anaerobic oral flora between late childhood and adolescence, or the formation of the deep tonsillar crypts after the regression of tonsillar tissue known to occur around this age. Either would cause the immune system to be first exposed to certain anaerobe infections only at this time, with a temporarily heightened risk of occasional invasive infection until adequate adaptive immunity is developed within a few years [23]. The potential role of Epstein-Barr Virus infection or thrombophilia, which display age distributions at least partially overlapping that of Lemierre syndrome, has never been proved conclusively because of limitations in the case definition, small sample sizes, poor case-mix, the absence of control groups, and the difficulty to exclude confounding [5,6,24].

The above-mentioned incidence studies identified cases based on positive cultures for *Fusobacterium necrophorum*, with the explicit exclusion of clinical cases of Lemierre syndrome with no growth of *Fusobacterium* even when they were documented [19], and in one study the case definition was further limited to a primary oropharyngeal focus [21]. As such, their figures only refer to the incidence of the "typical" definition and may underestimate the incidence of the condition in its broad clinical definition.

Several Authors have reported a decreased incidence of Lemierre syndrome between the 1950s and the 1970s, followed by a resurgence from the 1980s onwards [6]. These trends have been attributed to the increased use of antibiotic therapy in pharyngotonsillitis before the 1980s, followed by its progressive restriction in guidelines for primary care [21]; to the decreasing use of tonsillectomy [5]; or even to the disruption of nasopharyngeal flora by the introduction of pneumococcal vaccination [25]. Until recently, the claims of an increasing incidence were difficult to substantiate, as they were mainly based on the number of absolute reports in the scientific literature, single-centre series, or epidemiological studies of necrobacillosis (septicemia from *Fusobacterium necrophorum*) rather than Lemierre syndrome [26]. However, since 2000, the number of reported cases or publications also increased as a proportion of all scientific publications (as estimated by those reported on the Medline repository) [18]. The most recent nationwide study of *Fusobacterium*-associated cases confirmed an increasing trend from 2010 to 2017 in Sweden [22].

1.2. Clinical presentation, prognosis, and treatment

Most patients present with sepsis, neck swelling and tenderness, or both, typically a few days or weeks after an oropharyngeal illness. The latter has often already resolved by the time the patient's condition requires the medical attention that ultimately leads to diagnosis [6]. However, neither sepsis nor neck-specific signs and symptoms are highly sensitive or specific. Moreover, multi-organ involvement is already present at diagnosis, with over 80% of patients displaying septic embolism, especially pulmonary, musculoskeletal, or intracranial [18]. As a consequence, differential diagnosis is usually complex; depending on the dominant features at presentation, it may include conditions ranging from relatively common conditions such as streptococcal pharyngitis, viral infection (infectious mononucleosis, CMV), septic arthritis, meningitis, or community-acquired pneumonia [27,28] to leptospirosis, toxic shock syndrome, catastrophic anti-phospholipid antibody syndrome or systemic lupus erythematosus [29–32].

Frequently, the diagnosis is only considered after the incidental isolation of *Fusobacterium necrophorum*, which may lead to potentially clinically relevant delay of the appropriate management [33]. Therefore, a high index of suspicion is necessary to diagnose Lemierre syndrome. Awareness of the existence of the syndrome, especially in the setting of primary and acute care, may be essential to ensure a timely diagnosis. In the era of Internet and *Big Data*, prompt availability of large volumes of information or automated support to diagnosis may further contribute to the evolution of patterns of recognition and diagnosis.

Fatal outcome was common in the pre-antibiotic era. In the original series described by Lemierre, 18 out of 20 patients died. Subsequent series described decreasing fatality rates, with estimates over the last 20 years stable around 5% [18,34]. The analysis of cases described after 2000 provided the first estimates of the rate of in-hospital complications and long-term sequelae. More than 14% of the patients suffered new, recurrent, or worsening venous thromboembolism or peripheral septic lesions, whereas 12% of the survivors experienced post-discharge recurrence or clinical sequelae, including neurologic impairment such as cranial nerve palsy, blindness, paralysis or paresis, or orthopaedic and functional limitations. Patients with involvement of the central nervous system at baseline and those who did not receive anticoagulation therapy had more often in-hospital complications [18].

Over 90% of patients are treated with multiple antibiotics over their clinical course. Surgical treatment is often necessary, and internal vein ligation is still performed in cases with septic embolization refractory to medical therapy, albeit less often than in older series [18]. The use of anticoagulation in Lemierre syndrome has been the object of considerable controversy. While anticoagulant treatment is considered potentially valuable in containing the initial septic thrombus and to prevent extension or recurrence of venous thromboembolism, especially intracranially [35], clinicians often refrain from it because of the possibility that septic emboli may be unleashed from the primary thrombus, and because thrombocytopenia or tissue damage by septic emboli may increase the risk of bleeding. The most recent and largest analysis showed that the anticoagulant-related bleeding was sporadic, suggesting that Lemierre syndrome may not represent a specific trigger for bleeding complications [18]. Although these data were observational and do not permit any conclusion on causality or treatment efficacy, it is hard to find a rationale to depart from international guidelines suggesting in-hospital thromboprophylaxis for bedridden patient with an acute inflammatory disease and recommending routine anticoagulant treatment of acute venous thromboembolism. Any deviation from this approach should, in our opinion, represent an exception and be decided on an individual level basis until higher-level clinical evidence becomes available. This seems particularly appropriate in light of the apparently high rate of new thrombotic complications seen in hospitalized patients with Lemierre syndrome even after the initiation of antibiotic treatment.

2. The international Bacteria-Associated Thrombosis/ Thrombophlebitis and LEmierre syndrome (BATTLE) registry

2.1. Background and aims

The primary analysis of individual patient data of patients described after 2000 provided an estimate of the burden and clinical complexity of Lemierre syndrome in the contemporary era, confirmed it as an inherently thrombotic disease from a clinical standpoint, and established that its pathophysiological and clinical spectrum considerably overlap with other forms of bacteria-associated septic thrombophlebitis [7,17,18]. However, these findings may still be sensitive to reporting and detection bias. In order to provide guidance for patient management, they need to be integrated by higher-quality evidence as represented by a multicentre collection of consecutive patients, with cases identified based on a standardized definition, and relying on structured data entry. These data would serve to address several open issues in the clinical course of Lemierre syndrome, including the impact of key predictors of severity on patient outcomes, the patterns of involvement of vital organs – namely, the central nervous system, and the potential impact of anticoagulation. Such information would be especially useful in paediatric patients, for whom evidence is limited even on the overall diagnosis and management of acute venous thromboembolism. The epidemiological significance of Lemierre syndrome, its burden and its microbiological basis may also have far-reaching consequences on the clinical management of head/neck infections of adolescents and young adults in primary care. Current guidelines are still largely influenced by the priority of preventing rheumatic fever associated with group A β-haemolytic streptococcal pharyngitis; this goal may be outdated in light of the currently estimated incidence and severity of this condition, especially compared with the complications of *Fusobacterium* pharyngotonsillitis [36]. In this respect, a focused analysis of the overall burden of Lemierre syndrome in adolescents and young adults, including the long-term impact on survivors and its pharmacoeconomic implications, may provide a valuable contribution.

With these aims, we designed the Bacteria-Associated Thrombosis/ Thrombophlebitis and LEmierre syndrome (BATTLE) registry. Its ultimate goal is to improve the care of patients with bacterial thrombophlebitis, with a focus on Lemierre syndrome. Its primary objective is to advance the extent and level of the evidence that currently serves to guide clinical management, and support the development of guidelines and consensus documents. Specifically, the registry will

1. identify potential improvements in the diagnostic pathway, possibly leading to a reduced diagnostic delay;
2. identify clinically relevant prognostic tools for patients diagnosed with Lemierre syndrome;
3. evaluate the use of antibiotic therapies and anticoagulation treatment in Lemierre syndrome, both by directly providing real-world observational data and by generating information necessary to plan future interventional studies;
4. assess long-term functional status, quality of life, and self-sufficiency in survivors of Lemierre syndrome with a focus on standardized, validated patient-reported outcome measures.

2.2. Design

The BATTLE registry is a disease-specific, non-population based, multicentre clinical registry with ambispective, electronic data collection. It will include patients who satisfy the criteria for bacteria-associated thrombosis or thrombophlebitis or the subset of criteria for Lemierre syndrome (Table 1).

Its stakeholders will include patients, clinicians, researchers and scientific associations promoting research in thromboembolic, infectious, and paediatric diseases. Inclusion in the registry does not dictate any diagnostic or therapeutic interventions, and patients will be treated by applying current local or international guidelines at the discretion of the treating physicians.

The registry is designed in accordance with the recent recommendations of the experts of the RD-Connect project [37], which integrate field expertise with the FAIR framework for management and stewardship of scientific data [38] and the international guidelines provided by the United States Agency for Healthcare Research and Quality [39] and the European Commission's Joint Research Centre [40].

Data collection will be based on an electronic Case Report Form that secondarily collects information provided by the treating physician, and the main database maintained on a web-based infrastructure [41]. Its items include the European Commission's set of common data elements for Rare Diseases Registration [40] and are standardized based on the World Health Organization's international standards Anatomical Therapeutic Chemical Classification [42] and International Statistical

Table 1
General inclusion criteria of the BATTLE registry.

Bacteria-associated thrombophlebitis	Lemierre syndrome subgroup
1. Clinically diagnosed or microbiologically documented invasive bacterial infection	1. Clinically diagnosed or microbiologically documented invasive bacterial infection
2. History or objective diagnosis of primary infection focus in the head/neck or the abdominopelvic district	2. History or objective diagnosis of primary infection focus in head/neck district
3. Objective diagnosis of thrombosis in location anatomically adjacent to the primary infection focus and/or septic embolism in typical location	2. Objective diagnosis of thrombosis of the head/neck district or thromboembolism in locations anatomically consistent with the primary infection focus in the head/neck district

Classification of Diseases and Related Health Problems [43]. Quality assurance will be ensured by an integrity check upon data entry, quality control on periodic internal validation for clinical face validity and analytical internal validity.

2.3. Governance

The BATTLE registry is an independent, investigator-initiated study. The investigators are responsible for the design, conduct, and analysis of the registry data. The study has an academic sponsor (University Medical Center of the Johannes Gutenberg University, Mainz, Germany). Funding for its establishment and initial operational costs was provided by an award assigned by the *Gesellschaft für Thrombose- und Hämostaseforschung* (GTH) for the research project "Clinical presentation, treatment and course of Lemierre syndrome and bacterial-associated venous thromboembolism in children and adolescents". Ethical approval and registration on ClinicalTrials.gov are pending.

The registry's core team, its administrative support, and the main web-based portal (www.battle-registry.org) are based at the Center for Thrombosis and Hemostasis at the University Medical Center of the Johannes Gutenberg University of Mainz.

The registry complies with the principles of Ethical, Legal and Societal Issues [37]. Patient confidentiality will be ensured by pseudonymization, and separate informed consent will be provided as required. The reason of all patient withdrawals will be documented. If an informed consent for follow-up has been signed, the patient's family physician will be contacted if a personal contact is not possible. Transparency will be guaranteed by access rules and duties set forth in a publicly available statement of intellectual property and a Data Transfer Agreement.

2.4. Innovative features over available evidence

The BATTLE registry specifically addresses the limitations of current evidence on Lemierre syndrome and bacteria-associated thrombosis and thrombophlebitis. These conditions are rare, difficult to diagnose and of uncertain definition. As a consequence, available information is limited to case reports or single-centre series, which makes current evidence vulnerable to sampling, reporting, and publication bias. These issues have made it particularly difficult to draw definite conclusions on the role of potentially clinically relevant comorbidities and risk factors: in the absence of control groups, associations with risk factors were postulated or hypothesised based solely on their prevalence among observed cases, a form of *a posteriori* conditional probability that cannot prove association, much less causality or prediction, and is furthermore subject to detection bias [24]. Compared with other rare conditions, case finding of patients with septic thrombophlebitis is more complex and case-mix bias more likely, because their clinical presentation is non-specific and may include multi-organ involvement, with the medical specialties involved in their care varying by individual case, healthcare institution, and country; and because their clinical course is acute or subacute, with long-term follow-up of survivors possibly limited to subgroups with long-term sequelae or medical specialties outside critical and acute care. The following features of the BATTLE registry will address these limitations:

- **Comprehensive inclusion criteria** to make it possible to explore the whole spectrum of bacterial thrombophlebitis/Lemierre syndrome and thus compare the scientific merits of alternative epidemiological case definitions and the clinical value of alternative diagnostic criteria.
- **Ambispective design**: a structured first contact will allow new participating centres to first retrospectively include past patients satisfying the inclusion criteria, and subsequently prospectively include new patients upon diagnosis or upon regular contact by the core committee; this will minimise reporting and detection bias.
- **Global scale**: the study of rare diseases requires large networks in order for adequately sized samples to be reached, and poor geographic representativeness is thought to have particularly affected the study of Lemierre syndrome. [33] The existing network of the Lemierre study group, the sponsoring institution and the funding institutions, along with the absence of geographical limitations, will maximise the population size and its representativeness.
- **Multidisciplinary and multicentre network**: the involvement of secondary and tertiary care healthcare institutions and the outreach to all specialties potentially involved in the care of Lemierre syndrome (emergency medicine and critical care, infectious diseases, otolaryngology, microbiology, radiology, haematology, paediatrics, and general internal medicine) will enhance the representativeness of the registry population and prevent case-mix bias.
- **Active outreach and case-finding**: the core team will actively approach medical specialists belonging to specialties likely to see patients satisfying the inclusion criteria but who have so far reported none. This will be accomplished by the identification and active invitation of specialists in academic and non-academic hospitals, and by participation to scientific conferences of all specialties typically involved in the care of patients with septic thrombophlebitis.
- **Adherence to the FAIR data model (Findable, Accessible, Interoperable and Reusable)** will ensure transparency, access by external researchers, reproducibility of research findings, and compatibility with other databases.
- **Pre-defined compatibility with future prospective substudies** including long-term follow-up of patient-centred and patient-reported outcomes, which are largely absent from the evidence available so far, focused as it was on clinical outcomes.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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